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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/522,900	MCCORMICK ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/27/2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23,29 and 37-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23,29 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/8/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-23, 29 and 37-40 are pending.

Claim 3 has been amended.

2. Claims 1-23, 29 and 37-40 are under examination.

Objections/Rejections Withdrawn

3. The objection to the Oath/Declaration for not claiming priority to U.S. Provisional application 60/155,979 is withdrawn in view of the new Oath/Declaration filed 6/27/2002.

4. The rejection of claims 1-23, 29 and 37-40 under 35 U.S.C. 102(a) as anticipated by McCormick et al is withdrawn in view of the declaration filed 6/27/2002.

New Grounds of Rejections

Specification

5. The disclosure is objected to because of the following informalities:

The first line of the specification needs to be updated with a priority statement claiming priority to U.S. provisional application 60/155,979. For additional information on claiming benefit to an earlier filed application see United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application".

Appropriate correction is required.

Claim Objections

6. Claim 40 is objected to because of the following informalities:

Claim 40 is objected to for not containing a hyphen or the term "to" between 0.1 mg and 10 mg. Claim 40 should read "between about 0.1 mg-10 mg" or "between about 0.1 mg to 10 mg".

Appropriate correction is required.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-10 and 17-23 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to a polypeptide self-antigen that reads on polypeptide self-antigens that are found in nature such as Ig expressed on B cells of a lymphoma patient, for example. Thus, the invention lacks the hand of man.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 1-23, 29 and 37-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-23, 29 and 37-40 are indefinite for reciting "derived" in claim 1. The term "derived" is not one, which has a universally accepted meaning in the art nor is it one, which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of an ascertainable meaning for said phrase. Since it is unclear how the nucleic acid encoding the polypeptide self-antigen are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. In addition, since the term "derived" does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, chemically derivatized molecules, or even mimetics. In the absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

b. Claim 1 and those dependent upon claim 1 are indefinite for reciting "encoded at least in part" in claim 1. Does the nucleic acid encode only a part of the polypeptide self-antigen or is the entire polypeptide self-antigen encoded by the nucleic acid? Further, if only part of the polypeptide self-antigen is encoded by a nucleic acid, what part or parts of the polypeptide self-antigen is/are encoded by the nucleic acid?

c. Claim 1 and those dependent upon claim 1 are indefinite for reciting "at risk of developing a tumor, encoded at least in part by a nucleic acid in the cells of said tumor". It is unclear what is contemplated by the phrase "at risk of developing a tumor, encoded at least in part by a nucleic acid in the cells of said tumor" because a subject that is at risk of developing a tumor has not actually developed a tumor and thus, it is unclear if the polypeptide self-antigen (i.e., tumor-specific antigen) is actually encoded in the cells of a subject at risk of developing a tumor. Is the polypeptide self-antigen encoded only in the tumor cells (i.e., unique to tumor cells) of a subject or is the polypeptide self-antigen also expressed in normal cells of a subject at risk of developing a tumor?

d. Claim 20 recites the limitation "said subject". There is insufficient antecedent basis for this limitation in the claim. It is unclear what subject is being referred to in claim 20. Is the subject the mammalian host recited in claim 20 or is the subject the "subject with a tumor" or the "subject at risk of developing a tumor"? Further, it is unclear what is contemplated by the phrase "a mammalian host, including said subject". Is the administration to a mammalian host or to said subject or is the subject the mammalian host?

e. Claim 23 is indefinite in the recitation of "at least about" because there is no indication of the range of concentration of polypeptide to be administered. The phrase "at least about" is not defined in the specification and one of skill in the art could not determine the metes and bounds of the claim. See MPEP 2173.05(b).

f. Claim 23 recites the limitation "said polypeptide antigen". There is insufficient antecedent basis for this limitation in the claim. It is unclear which polypeptide antigen

claim 23 refers to. Does the phrase "said polypeptide antigen" mean the polypeptide self-antigen or the scFv comprising the variable domains of the surface Ig of B cell lymphomas?

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-23, 29 and 37-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a B-cell lymphoma surface immunoglobulin antigen (i.e., idiotype) useful in the treatment of a subject having a B-cell lymphoma, wherein the B-cell lymphoma surface immunoglobulin antigen is expressed in a cell or organism or a plant as a scFv and an immunogenic composition or therapeutic composition comprising a B-cell lymphoma surface immunoglobulin antigen useful for inducing a tumor-specific immune response, does not reasonably provide enablement for (a) a B-cell lymphoma surface immunoglobulin antigen (i.e., idiotype) useful in the treatment of a subject at risk of developing a B-cell lymphoma, wherein the B-cell lymphoma surface immunoglobulin antigen is expressed in a plant as a scFv (b) just any polypeptide self-antigen useful for treating a subject having a B cell lymphoma or a subject at risk of developing a B cell lymphoma; (c) just any polypeptide self-antigen useful for treating a subject having just any tumor or a subject at risk of

developing any tumor; (d) a B-cell lymphoma surface immunoglobulin antigen useful for treating a subject having just any tumor or a subject at risk of developing any tumor, wherein the polypeptide self-antigen or B-cell lymphoma surface immunoglobulin antigen expresses just any epitope and vaccine compositions useful for inducing a tumor-specific immune response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or

lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The nature of the invention: The claims of the instant invention are broadly drawn to any polypeptide self-antigen that is useful as a vaccine to treat any tumor, wherein the polypeptide is any epitope expressed on a tumor (claims 1-4), and the polypeptide is produced by a cell or organism that has been transformed with a nucleotide sequence derived from a tumor of a subject.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that B-cell lymphomas express Ig molecules on the surface of the cell. These Ig molecules can be utilized as potential B-cell tumor markers, and as such, anti-idiotypic antibodies that are either whole antibodies or antibody fragments that recognize idiotypes on the surface expressed Ig molecules can used as an antigen, eliciting the immune response against the B-cells expressing such Ig molecules on their surfaces (see Casper *et al* (Blood 1997; 90(9):3699-3706) and McCormick *et al* (PNAS USA 1999;96:703-708)). The art also teaches that products, that are intended as cancer vaccines, are challenging and perhaps impossible wherein the "notion that cancer vaccines will replace standard therapeutic strategies in malignant disease still belongs to the realm of fiction." (Evans et al, Q J Med, 92:299-307, 1999, see page 303). According to Donnelly J. (Nature Medicine, 11(9): 1354-1356, Nov. 2003) "treating cancer with something that looks more like a modern-day vaccine, with a defined antigen and an optimized adjuvant and delivery platform, is still in the future"

(see page 1354 lines 13-17). Further, DeGruijl T. D. (Nature Medicine, 5(10): 1124-1125, Oct. 1999) teach that a variety of anti-tumor vaccine trials have been undertaken and in spite of the large number of these trials, and the plethora of distinct approaches investigated, there has been little evidence of clinical efficacy. DeGruijl also states "precise correlates of clinical effects and immunological responses have been lacking" (see page 1124, left column). Thus, Applicant is not enabled for any vaccine composition.

The amount of direction or guidance present and the presence or absence of working examples: The instant specification has taught the isolation of polynucleotide sequences encoding VH and VL regions of a surface expressed Ig molecule from bone marrow aspirates by RT-PCR. The specification also discloses the generation of a polynucleotide sequence encoding an scFv to be used as an antigen to elicit a polyclonal antibody immune response for the treatment of B-cell lymphomas. The specification does not teach any other polypeptide self antigens other than scFvs constructed from the VH and VL domains of Ig expressed on the surface of B cell lymphomas that are useful for treating a subject having a B cell lymphoma or for treating a subject risk of developing a B cell lymphoma. Furthermore, the specification does not teach just any polypeptide self-antigen useful for treating a subject having just any tumor or at risk of developing just any tumor. As a result, one of skill in the art would not be able to practice the invention commensurate in scope with the claims without undue experimentation. Again, the teachings in the specification are limited to a polynucleotide encoding a scFv, which is one type of epitope found on the surface of a

specific type of tumor, namely, B-cell lymphomas. The specification has also not taught any vaccine or method of treating any subject at risk of developing a tumor because it is difficult to determine the population that would be at risk of developing a tumor and the skilled artisan would be forced into undue experimentation to determine the population that would be predisposed to developing just any tumor or even B cell lymphomas.

The breadth of the claims and the quantity of experimentation needed: Given the broad range of peptides, tumors and patient population encompassed within the claims, which includes any polypeptide self-antigen, any tumor type, including tumors that don't necessarily express the polypeptide self-antigen or a surface Ig, and patient populations that are at risk of developing a tumor, and absent sufficient teachings in the specification to overcome the teachings of unpredictability found in the art, it would require undue experimentation by one of ordinary skill in the art to be able to practice the invention commensurate in scope with the claims.

13. Claims 1-11, 17-23, 29 and 37-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a B-cell lymphoma surface immunoglobulin antigen (i.e., idiotype) and an immunogenic composition or therapeutic composition comprising said B-cell lymphoma surface immunoglobulin antigen comprising both VH and VL domains, wherein the VH and VL domains comprise 6 CDRs, three from the VH domain and three from the VL domain, does not reasonably provide enablement for a B-cell lymphoma surface immunoglobulin antigen and an immunogenic composition or therapeutic composition comprising said B-cell

lymphoma surface immunoglobulin antigen comprising two VH domains (VH-VH) or two VL domains (VL-VL) (see claim 7), or comprising part of the VH and part of the VL or less than the full-complement of CDRs (i.e., only CDR2; claims 9-10) from both the VH and VL chains as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a B-cell lymphoma surface immunoglobulin antigen and an immunogenic composition or therapeutic composition comprising said B-cell lymphoma surface immunoglobulin antigen comprising two VH domains (VH-VH) or two VL domains (VL-VL), part of the VH and part of the VL and less than the full-complement of CDRs (i.e., only CDR2; claims 9-10) from both the VH and VL chains. The claim language encompasses two VH domains (VH-VH) and two VL domains (VL-VL), fragments of the VH and VL domains, which do not contain a full set of 6 CDRs and would not form idotypes, which are conformational-dependent epitopes.

The specification discloses that an idiotype or epitope thereof formed by the association of the CDRs of both the VH and VL domains. The specification does not enable an idiotype that is formed by the association of two VH domains (VH-VH) or two VL domains (VL-VL) or less than the full complement of CDRs from both the VH and VL domains or fragments of the VH and VL domains.

The claims encompass a B-cell lymphoma surface immunoglobulin antigen or idiotype and an immunogenic composition or therapeutic composition comprising said B-cell lymphoma surface immunoglobulin antigen or idiotype comprising two VH domains (VH-VH) or two VL domains (VL-VL) or part of the VH and part of the VL or less than the full-complement of CDRs (i.e., only CDR2; claims 9-10) from both the VH and VL chains. Benvenuti et al (Gene Therapy, 8(20):1555-1561, October 2001) teach that scFv DNA vaccination results in a highly specific anti-idiotypic immune response that strictly depends on the quaternary structure of the idiotype (see page 1559, right column). "The anti-idiotype immune response was directed exclusively at the original immunising VL/VH combination, with complete absence of antibodies recognizing determinants in any of the single V regions displayed in the context of a different idiotype." (Benvenuti et al, see page 1558). Thus, Benvenuti et al demonstrate that the parental V regions association is an absolute requirement to induce anti-idiotype antibodies and these antibodies are exclusively against conformational combined VL/VH determinants (see page 1557 and abstract). Thus, it is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences, which maintain their required conformation, are required in order to produce

anti-idiotype antibodies that bind conformation dependent idiotypes expressed on B cell lymphomas. It is unlikely that an idiotype or an immunogenic composition or therapeutic composition comprising said idiotype, which comprises two VH domains (VH-VH) or two VL domains (VL-VL) or only part of the VH and part of the VL or less than the full-complement of CDRs (i.e., only CDR2; claims 9-10) from both the VH and VL chains as defined by the claims, have the required conformational combined VL/VH determinants or epitopes (i.e., idiotypes). Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of using an idiotype useful in the treatment of B-cell lymphomas and an immunogenic composition or therapeutic composition comprising said idiotype for inducing a tumor-specific immune response, wherein said idiotype comprises only part of the VH and part of the VL or less than the full-complement of CDRs (i.e., only CDR2; claims 9-10) from both the VH and VL chains. One of skill in the art would neither expect nor predict the appropriate functioning of the idiotype as broadly as is claimed.

Therefore, in view of the lack of guidance in the specification and in view of Benvenuti et al, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to using an idiotype useful in the treatment of B-cell lymphomas and an immunogenic composition or therapeutic composition comprising said idiotype for inducing a tumor-specific immune response, wherein said idiotype comprises only part of the VH and part of the VL or less than the full-complement of CDRs. Undue experimentation would be

required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-13, 17-22, 29 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Casper et al (Blood, 90(9):3699-3706, November 1997).

The claims are drawn to a polypeptide self-antigen useful as a tumor specific vaccine in a subject with a tumor or in a subject at risk of developing a tumor, wherein: (1) the epitope is unique to or over expressed by the tumor cells, (2) the polypeptide is produced in a cell or organism transformed by the nucleic acid, (3) the polypeptide is obtained from the transformed cell or organism in correctly folded form, and (4) the polypeptide self-antigen is capable of inducing an immune response. Further, the polypeptide self-antigen has at least two peptide domains, wherein said tumor is a B-cell lymphoma and said epitope is a surface Ig epitope, wherein said polypeptide comprises at least one idiotypic epitope of the V region of said surface Ig, wherein there are at least two V regions of which at least part of the VH and VL are also domains of the said Ig, wherein the VH region has a CDR, which is CDR2, wherein the polypeptide

is a two domain scFv that includes (i.e., comprises) VH and VL domains, wherein the VH and VL domains are linked by an amino acid linker between 1 and about 50 residues and facilitates the secretion and correct folding of said polypeptide to mimic the tumor epitope in its native form in or on said tumor cell and the polypeptide self-antigen is in solution, integrated into a carrier, induces a protective anti-tumor immune response, induces a polyclonal anti-idiotypic antibody response or a cell mediated immune response and wherein the antibody response is measured by testing serum or peripheral blood cells of the host in an enzyme immunoassay or by flow cytometry. Claim 29 is drawn to a vaccine composition comprising the polypeptide self-antigen (i.e., scFv) and a pharmaceutically acceptable carrier or excipient and further comprises a cytokine or a chemokine (claim 38).

Casper et al teach the use of an idiotype for the treatment of B-cell lymphoma, wherein the idiotype mimics a surface Ig molecule (see entire document). Casper et al further teach the production of the polypeptide in a cell which was transformed by a nucleotide sequence that encoded the polypeptide, which was able to induce a cell mediated immune response (i.e., Th1) as well as polyclonal antibodies (see page 3701, right column, page 3704, right column and Figure 4). Casper et al also teach a polypeptide (i.e., scFv) that has at least two domains of at least one idiotypic epitope and comprises a VH and a VL domain that are from the B cell surface Ig molecule and said VH and VL domains are linked by a linker that is 16 amino acids in length (see Figure 1). Because the scFv (idiotype) was produced and induced the production of polyclonal antibodies that are reactive with the surface Ig on B cell lymphomas, it is

inherent that the linker facilitates secretion and correct folding of the scFv to mimic the native form of the surface Ig (i.e., tumor epitope) expressed on the surface of B cell lymphomas. Also, since the scFvs taught by Casper et al contained the complete VH domain, it is inherent that the complete VH domain includes CDR2, absent evidence to the contrary. Casper et al teach that the administration of scFv in a PBS solution (i.e., integrated into a carrier; pharmaceutically acceptable carrier or excipient) that was able to elicit an anti-tumor immune response, wherein the anti-tumor immune response is measured from collected sera in an ELISA (see Figure 3). Casper et al also teach a scFv-GM-CSF fusion, wherein the GM-CSF is an immunostimulatory cytokine (claim 39) (see Figure 1).

Applicant is reminded that all that is required of the reference is that it sets forth the substance of the invention. The intended use recitations such as useful as a tumor-specific vaccine in a subject with a tumor or at risk of developing a tumor and a vvaccine composition useful for inducing a tumor-specific immune response are given no patentable weight. Further, it is noted that the phrase "capable of" (see claim 1, part d) is non-limiting because an element "capable of" performing a function is not a positive limitation, but only requires the ability to so perform. Further the instantly claimed polypeptide self-antigen "includes", which is open claim language, meaning that the polypeptide comprises the VH and VL domains as well as additional domains or elements such as the scFv-GM-CSF fusion protein taught by Casper et al. Additionally, claims 1 (parts b and c) and 2-3 are drafted in the product-by-process format. The reference does not describe the production of the molecule using the methods identical

to that is recited in claims 1 (parts b and c) and 2-3. However, the recitation of a process limitation in claims 1 (parts b and c) and 2-3 are not viewed as positively limiting the claimed product absent a showing that the process of making recited in claims 1 (parts b and c) and 2-3 imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon the applicants to establish a patentable distinction between the claimed and references products.

16. Claims 1-12, 17-23, 29 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Hawkins et al (WO 94/08008, 4/14/1994).

The claims have been described supra.

Claim 23 recites wherein the administration comprises subcutaneous immunization with at least about 15 μg of said polypeptide self-antigen three times about two weeks apart.

Hawkins et al teach a scFv that is an idiotypic determinant of an immunoglobulin expressed on the surface of a B cell lymphoma (see entire document, particularly Figure 1 and pages 2-8). Thus, the scFv includes an epitope that is unique to B cell lymphoma cells, includes the VH and VL domains, which are two peptide domains, two V region domains, are at least part of the VH and part of the VL and includes CDR2 (i.e., at least one CDR). Hawkins et al teach the scFv in PBS (i.e., integrated into a carrier; in solution; a pharmaceutically acceptable carrier or excipient) administered to a mammalian host by subcutaneous immunization at 12.5 μg three times about two

weeks apart (see page 19). 12.5 μg of the scFv is interpreted to be at least about 15 μg. Hawkins et al teach that administration of the scFv generated a polyclonal anti-idiotypic antibody response, which was detected by testing the sera of the host by ELISA (enzyme immunoassay) and flow cytometry (FACS analysis) (see pages 20-21 and 7). Also, since the scFvs taught by Hawkins et al contained the complete VH domain, it is inherent that the complete VH domain includes CDR2, absent evidence to the contrary. Finally, Hawkins et al teach that the scFv (i.e., altered self polypeptide) may be co-administered with an immunomodulatory cytokine (see pages 2-3).

Applicant is reminded that all that is required of the reference is that it sets forth the substance of the invention. The intended use recitations such as, "useful as a tumor-specific vaccine in a subject with a tumor or at risk of developing a tumor" is given no patentable weight. Further, the phrase "capable of" (see claim 1, part d) is non-limiting because an element "capable of" performing a function is not a positive limitation, but only requires the ability to so perform. Additionally, claims 1 (parts b and c) and 2-3 are drafted in the product-by-process format. The reference does not describe the production of the molecule using the methods identical to that is recited in claims 1 (parts b and c) and 2-3. However, the recitation of the process limitations in claims 1 (parts b and c) and 2-3 are not viewed as positively limiting the claimed product absent a showing that the process of making recited in claims 1 (parts b and c) and 2-3 imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is placed upon Applicant to establish a patentable distinction between the claimed and references

products.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 1-23, 29 and 37-40 are rejected under 35 U.S.C.103(a) as being unpatentable over Caspar et al (Blood, 90(9):3699-3706, November 1997) in view of Fiedler et al (Immunotechnology, 3(3):205-216, October 1997, Ids filed 3/8/04) and Tang et al (Journal of Biological Chemistry, 271(26):15682-15686, June 1996) and Hakim et al (Journal of Immunolgoy, 157:5503-5511, 1996).

AS APPLIED TO CLAIMS 1-13, 17-22, 29, 38 ABOVE

Claims 1-13, 17-23, 29 and 38 have been described supra.

Claims 14-16 further limit the linker connecting the VH and VL domains wherein the linker is a member of a randomized library of linkers with the following requirements: position 1 cannot be the same nucleotide as position 2 of a repeated triplet, position 2 cannot be the same nucleotide as position 3 of a repeated triplet, and position 1 cannot be the same nucleotide as position 3 of a repeated triplet (claim 14), wherein the nucleotide in the first and second positions of each repeated triplet is selected from any two of dA, dG, dC or dT (claim 15) and wherein the linker at position 1 is dA or dG, position 2 is dC or dG, and position 3 is dT (claim 16).

Claims 37 further limits the vaccine composition as comprising an adjuvant, claim 38 recites wherein the cytokine is selected from the group consisting of IL-1, IL-2, IL-12, IL-18 and interferon-gamma. Claim 40 is interpreted as further limiting the vaccine composition, wherein the excipient is sterile saline and wherein each unit dosage is between 0.1 mg-10 mg of the polypeptide self-antigen.

Caspar et al teach a scFv obtained from a B-cell lymphoma Ig surface antigen. Because the scFv taught by Caspar et al is a scFv, it has two V-regions, one VH and one VL, wherein the VH region (see Figure 1, for example) includes at least one CDR,

wherein it is a CDR2 (see page 3700) and is comprised of at least two domains. Furthermore, Caspar et al teaches that the scFv is linked together by a linker sequence. Moreover, Caspar et al teaches that although weak, the scFv administered did induce an immune response (see page 3702, 2nd column). Caspar et al does not specifically characterize the scFv, nor does he specifically teach a randomized library of linkers with the instantly claimed criteria or a ~~vaccine~~ composition comprising an adjuvant or Il-1, Il-2, IL-12, IL-18 or interferon-gamma or wherein the excipient is sterile saline and wherein each unit includes between about 0.1 mg–10 mg of the polypeptide self-antigen. These deficiencies are made up for in the teachings of Fiedler et al and Tang et al and Hakim et al.

Fiedler et al teach that scFv can be made in high quantities in transgenic plant cells, wherein 4-6% to 3-4% of the total protein found in leaves and seed, respectively, can be recombinantly expressed scFv. Furthermore, Fiedler et al teach that such recombinant scFv is functionally active.

Tang et al teach that a linker suitable for one scFv will not be optimal for other scFvs and linker length and sequence affect the expression level, solubility, stability and binding affinity of the scFvs (see page 15682, right column). Tang et al teach a method of selecting active scFvs synthesized form libraries of scFv genes with randomized linker DNA sequences (see abstract and pages 15682-15684).

Hakim et al teach immunotherapeutic compositions comprising a scFv constructed from the Ig variable regions from B cell lymphomas (i.e., idiotype) for inducing a polyclonal anti-idiotype response (see entire document). Hakim et al teach

that the scFv needed to be conjugated to a strong carrier such as keyhole limpet hemocyanin (KLH) and mixed with an adjuvant to induce a tumor-protective anti-idiotypic response (see page 5503, left column). Hakim et al also teaches that scFv-Il-2 and scFv-IFN-gamma as well as others enhanced the immunogenicity of the idiotype and elicited and anti-idiotype response that was protective against tumor challenge (see page 5503, right column).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce a scFv comprising B-cell Ig epitopes for therapeutic benefit of B cell lymphomas as taught by Caspar et al, wherein the scFv comprises VH and VL domains linked by a randomized linker as taught by Tang et al and to combine the scFv with an adjuvant or IL-2 or IFN-gamma to enhance the immunogenicity of the scFv (idiotype) and elicit an anti-scFv (anti-idiotype) response that would be protective against tumor challenge as taught by Hakim et al and to have produced the scFv in a plant as taught by Fiedler et al. One of skill in the art would have been motivated in doing so because Caspar et al teach the extraction and isolation of an antibody or Ig obtained from a B-cell lymphoma and the VH and VL domains of the surface Ig molecule are linked together with a linker and Tang et al teach a method of selecting active scFvs synthesized form libraries of scFv genes with randomized linker DNA sequences. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have optimized the scFv linker because Tang et al teach that a linker suitable for one scFv will not be optimal for other scFvs and linker length and sequence affect the expression level, solubility,

stability and binding affinity of the scFvs, and the skilled artisan would have had a reasonable expectation of success because the scFvs with randomized linkers taught by Tang et al were functionally active. Further, it would have been obvious to the skilled artisan at the time the invention was made to use the scFv with an adjuvant or as a scFv-IL-2 or scFv-IFN-gamma fusion protein to enhance the immunogenicity of the scFv and elicit an anti-scFv response (anti-idiotype response) that would be protective against tumor challenge as taught by Hakim et al and the skilled artisan would have been motivated to optimize the dosages and administration of the scFv for optimum therapeutic benefit of B cell lymphomas. In addition, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce a scFv comprising B-cell Ig epitopes for therapeutic benefit of B cell lymphomas as taught by Caspar et al, wherein the scFv comprises VH and VL domains linked by a randomized linker as taught by Tang et al and to combine the scFv with an adjuvant or IL-2 or IFN-gamma to enhance the immunogenicity of the scFv (idiotype) and elicit an anti-scFv (anti-idiotype) response that would be protective against tumor challenge as taught by Hakim et al and to have produced the scFv in a plant as taught by Fiedler et al because Fiedler et al teach that plant expression of scFvs offers a number of advantages including no requirement for complex culture media, sterility or large culture vessels, the possibility of composting plant waste material, no contamination with mammalian viruses or bacterial endotoxins, the latter two are especially important for producing scFvs intended for therapeutic use (see page 206, left column). Furthermore, Fiedler et al teach that plant material offers stable short- or long-term storage of scFvs

and is advantageous if the harvested material has to be transported or stored before further processing. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce a scFv comprising B-cell Ig epitopes for therapeutic benefit of B cell lymphomas as taught by Caspar et al, wherein the scFv comprises VH and VL domains linked by a randomized linker as taught by Tang et al and to combine the scFv with an adjuvant or IL-2 or IFN-gamma to enhance the immunogenicity of the scFv (idiotype) and elicit an anti-scFv (anti-idiotype) response that would be protective against tumor challenge as taught by Hakim et al and to have produced the scFv in a plant as taught by Fiedler et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

19. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

20. Claims 1-23, 29 and 37-40 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-23, 29 and 37-40 of copending

Application No. 10/067,790. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

21. Claims 1-23, 29 and 37-40 of this application conflict with claims 1-23, 29 and 37-40 of Application No. 10/067,790. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Conclusion

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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LARRY R. HELMS, PH.D
PRIMARY EXAMINER